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EXAMINER

HINES, J

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PAPER NUMBER

1645

8

DATE MAILED:

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**Please find below and/or attached an Office communication concerning this application or proceeding.**

**Commissioner of Patents and Trademarks**

# Office Action Summary

Application No.  
**09/336,036**

Applicant(s)

**Schllevert et al.**

Examiner

**Ja-Na Hines**

Group Art Unit  
**1645**



☒ Responsive to communication(s) filed on Jun 18, 1999

☐ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 35 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

## Disposition of Claim

☒ Claim(s) 1-16 is/are pending in the application

Of the above, claim(s) 11-16 is/are withdrawn from consideration

☐ Claim(s) \_\_\_\_\_ is/are allowed.

☒ Claim(s) 1-10 is/are rejected.

☐ Claim(s) \_\_\_\_\_ is/are objected to.

☒ Claims 1-16 are subject to restriction or election requirement.

## Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on \_\_\_\_\_ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on \_\_\_\_\_ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

## Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some\* ☒ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) \_\_\_\_\_

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

\*Certified copies not received: \_\_\_\_\_

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

## Attachment(s)

☒ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). 8

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

— SEE OFFICE ACTION ON THE FOLLOWING PAGES —

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## DETAILED ACTION

### *Election/Restriction*

1. Restriction to one of the following inventions is required under 35 U.S.C. 121:
  - I. Claims 1-10 are drawn to a mutant SPE-C toxin, classified in class 424, subclass 93.44.
  - II. Claims 11-12 and 15-16 are drawn to a vaccine, pharmaceutical composition, method of protection and method of reducing symptoms classified in class 424, subclass 184.1.
  - III. Claims 13-14 are drawn to DNA sequence and host cell, classified in class 435, subclass 252.3.
2. The inventions are distinct, each from the other because of the following reasons:

Inventions I and II or III are related as product and process of use. The inventions can be shown to be distinct if either or both of the following can be shown: (1) the process for using the product as claimed can be practiced with another materially different product or (2) the product as claimed can be used in a materially different process of using that product (MEP. § 806.05(h)).

In the instant case Group I is a mutant toxin and this toxin can be used with many other uses. The toxin can be used to indicate infection, or create antibodies. Further, other products in the art can be used to make DNA, as in Group II or a vaccine, as recited in Group III.

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3. Because these inventions are distinct for the reasons given above and have acquired a separate status in the art as shown by their different classification, restriction for examination purposes as indicated is proper.

4. Because these inventions are distinct for the reasons given above and the search required for Group I is not required for Group II or III, restriction for examination purposes as indicated is proper.

5. During a telephone conversation with Mark Skoog on September 14, 2000 a provisional election was made without traverse to prosecute the invention of Group I, claims 1-10.

Affirmation of this election must be made by applicant in replying to this Office action. Claims 11-16 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

6. Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a petition under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(I).

### ***Specification***

7. The lengthy specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which applicant may become aware in the specification.

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***Claim Rejections - 35 USC § 112***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

8. Claims 1-10 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for Streptococcal pyrogenic exotoxin type C (SPE-C), does not reasonably provide enablement for altering the amino acid sequence by any insertion, deletion or substitution of one more amino acid. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

The claims and specification recite mutant to mean any SPE-C that is not completely identical to the wild-type SPE-C, and that a mutant can be obtained by deletion, substitution or insertion of one or more amino acids, however that specification only provides guidance to specific amino acids and does not teach all amino acids changes that may or may not be changed without causing a detrimental effect to the peptidase to be produced. The claims broadly teach at least one amino acid deletion, substitution or insertion, therefore any amino acid is being claimed, and no specific location for where the deletion, substitution or insertion or any

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combination thereof is recited, if all the amino acids are deleted or substituted or inserted the resulting mutant SPE-C could result in a mutant toxin not taught and enabled by the specification.

The specification does not provide substantive evidence that the claimed vaccines which broadly teach the deletion, substitution or insertion of any amino acid is being claimed is capable of inducing protective immunity. This demonstration is required for the skilled artisan to be able to use the claimed vaccines for their intended purpose of preventing Streptococcus infections. Without this demonstration, the skilled artisan would not be able to reasonably predict the outcome of the administration of the claimed vaccines, i.e. would not be able to accurately predict if protective immunity has been induced by any mutant of SPE-C.

Thomas E. Creighton, in his book, "Proteins: Structures and Molecular Properties, 1984", (pages 314-315) teaches that variation of the primary structure of a protein can result in an instable molecule. He teaches that a single amino acid change can cause a mutant hemoglobin to have lower stabilities due to any of several causes:

- 1) alteration of close-packing of the interior; loss of one group that normally participates in a hydrogen bond or salt bridge;
- 2) the introduction of a charged or polar group into the interior or the insertion into a helical region of a Proline residue, which must distort the alpha-helix;
- 3) while sometimes radical changes of surface groups, even introduction of a non-polar side chain- have no great effect on stability.

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Thomas E. Creighton, in his book "Protein structure: A Practical Approach, 1989; pages 184-186" teaches that present day site directed mutagenesis of a gene allows any amino acid in a protein sequence to be changed to any other, as well as introducing deletions and insertions. The reference goes on to teach that it is difficult to know which amino acid to change and which is the best residue to substitute for the desired functional and structural effect.

Nosoh, Y. et al in "Protein Stability and Stabilization through Protein Engineering, 1991" (chapter 7, page 197, second paragraph) adds support to Thomas E. Creighton, by teaching that results so far accumulated on the stability and stabilization of proteins appear to indicate that the strategy for stabilizing proteins differ from protein to protein and that any generalized mechanisms for protein stability have not yet been presented.

The substitution of any amino acid in any location within the mutant SPE-C would not predictably result in a stable molecule. The specification only teaches the use of specific amino acids in specific locations which result in stable variations. The specification does not provide guidance on how any amino acid can be deleted, substituted or inserted for the production a stable bacterial SPE-C nor does the specification provide guidance on how any location can be used to produce a stable protein. No working examples are shown containing the missing information. Without such information, one of skill in the art could not predict which deletions, substitutions or insertions or any combination thereof would result in the desired stable, active protein. Accordingly, one of skill in the art would be required to perform undue experimentation

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to use any amino acid at any location to produce a stable SPE-C toxin. Therefore, one skilled in the art could not make and/or use the invention without undue experimentation.

9. Claims 1-10 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Acronyms like SPE-C must be spelled out when used for the first time in a chain of claims.

10. The recitation of “substantially nonlethal compared with a protein substantially corresponding to the wild type SPE-C toxin” in claim 1 is vague. The term substantially is not defined by the claims or specification such that one skilled in the art would be able to ascertain what level “substantially” would represent. Further, it is unclear how to determine how substantial nonlethal and the correspondence need to be with respect to the wild type toxin.

11. Claims 3-9 are unclear. The specification, in example 6 and claims 3-9 refer to the mutant SPE-C having an amino acid change at amino acid asparagine 38, however, the description at page 11, line 24 and Table 2 cite the substitution at asparagine 37. Applicant is required to explain the discrepancy.

12. Claim 10 recites substantially enhance endotoxin shock, therefore has the same problems as Claim 1, see above.



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***Claim Rejections - 35 USC § 102***

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

13. Claim 1 is rejected under 35 U.S.C. 102(b) as being anticipated by Goshorn et al.

Goshorn et al., teaches the nucleotide sequence of Streptococcal Pyrogenic Exotoxin type C and found that the SPE-C had the greatest sequence homology with SPE-A (abstract). SPE-C is a member of a family of biologically and biochemically related toxins produced by *Streptococcus pyogenes* and *Staphylococcus aureus* (page 2518). The toxins occur in three serologically distinct forms, A, B and C and have been associated with streptococcal toxic shock-like diseases (page 2518). The authors have also previously reported the cloning of the gene for SPE-C where the gene was localized, DNA fragments were ligated to bacteriophages, transformed in *E. coli* and recombinant phages were selected (page 2518). Deletion subclones were obtained using exonuclease activity and further suggest using site-directed mutagenesis to analyze the toxin (page 2518). The SPE-C amino acid sequence was found to be highly related to SPE-A sequences and found to have a high degree of similarity by allowing conservative amino acids changes (page 2519, Table 1 and Figure 2). The amino acid alignments reveal some clusters of conservation particularly in the carboxyl halves of the proteins, however the regions may

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represent biologically important sites necessary for the structural integrity of the proteins (page 2519).

Therefore, Goshorn et al., teaches a mutant SPE-C toxin with at least one amino acid change as compared to the wild-type SPE-C.

***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

14. Claims 1-10 are rejected under 35 U.S.C. 103(a) as being unpatentable over Goshorn et al., in view of Kline et al. Goshorn et al., has been discussed above, however, Goshorn does not teach specific amino acid changes.

Kline et al., teaches the analysis of the superantigen activity of mutant and allelic forms of SPE-A. Bacterial superantigens associated with food poisoning and or associated with Toxic Shock Syndrome 1 and 2 or the streptococcal toxins SPE-A, SPE-B and SPE-C are known for their ability to overstimulate the host immune system (page 866). The authors generated 20 mutant forms of SPE-A and the mutant toxins were analyzed for mitogenic stimulations of human peripheral blood formulations and the residues necessary for each function was identified (abstract). Mutational analysis of SPE-A was done in order to define the regions of the toxin

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important for this activity, hence 20 mutants forms were analyzed for their mitogenic activity and their affinity for class II MHC molecules (page 861-862). Also, the important of a potential disulfide loop in the ability of the toxin to stimulate immunocytes and bind to class II MHC molecules was evaluated (page 832). The Materials and Methods section teaches the construction of a transformed host cell, DNA sequences encoding SPE-A, generations of point mutations in SPE-A, mitogenicity assays and determination of the structure of SPE-A. The positions of the 20 additional amino acids substitutions are shown in Figure 2, 16 of the residues were chosen based on the fact that these residues are known to be important for activity of the closely related bacterial superantigen SPE-B (page 863). An example substitution was at position 12 to an alanine residue (page 863). Figure 3 shows the mitogenic activities of the SPE-A mutants and Figure 4 shows the mitogenic activities at mutant and allelic forms of SPE-C as compared to recombinant SPE-A.

Therefore, it would have been obvious at the time of applicants invention to have used the mutant SPE-C as taught by Goshorn et al., in the method of Kline et al., because Goshorn et al., teaches that SPE-C has the greatest sequence homology with SPE-A wherein the amino acid alignments reveal some clusters of conservation and the regions may represent biologically important sites necessary for the structural integrity of the proteins and SPE-C is a member of a family of biologically and biochemically related toxins produced by *Streptococcus*.

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15. Claims 1-10 are rejected under 35 U.S.C. 103(a) as being unpatentable over Goshorn et al., in view of Hartwig et al. Goshorn et al., has been discussed above, however, Goshorn does not specifically teach mutant proteins.

Hartwig et al., teaches streptococcal pyrogenic exotoxin A (SPEA) is an important pathogenicity factor of group A streptococci and it is a member of the family of super antigens (abstract). The authors have generated nine mutant SPEA molecules by substituting amino acids in the regions of homology between different streptococcal and staphylococcal superantigens (abstract). Additional mutants were also created by deletion of the 10 N-terminal amino acids (abstract). Several mutations created lead to loss of function but do not affect the binding of neutralization antibodies (page 869). The Methods section teaches introduction of single point mutations into the *speA* gene and the expression and purification of the recombinant SPEA proteins (page 870). Figure 1 shows the location of amino acids substitutions in the different mutants of SPEA. Figure 3 shows the mitogenic activity of mutant SPEA molecules. Some of the results show that the replacement of amino acid residues within the conserved regions of SPEA does not affect the expression of two individual neutralizing epitopes (page 874). Other studies using mutagenesis of toxin genes had been published, where some have substituted with cysteine or alanine (page 874). The residue Lys-138 is not part of the alpha5 groove and therefore is not directly involved in the class II interaction. The mutants are still able to induce such neutralizing antibodies and could be used for vaccination purposes (page 875).

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Therefore, it would have been obvious at the time of applicants invention to have used the SPE-C which has the greatest sequence homology with SPE-A as taught by Goshorn et al., with the mutations and vectors taught by Hartwig et al., because Hartwig et al., teaches mutant SPE molecules by substituting and deleting amino acids where several mutations created lead to loss of function but do not affect the binding of neutralization antibodies.

***Prior Art***

16. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. Hovde et al., teaches the investigational role of the disulfide bond in the activity and structure of Staphylococcal enterotoxin C1. Goshorn et al., (Mol. Gen. Genet.) Teaches the cloning and characterization of the SPE-C gene for *Streptococcus pyogenes*. Norrby-Teglund et al., teach the detection and nucleotide sequence analysis of the SPE-C gene in Group A Streptococcal isolates.

17. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ja-Na Hines whose telephone number is (703) 305-0487. The examiner can normally be reached on Monday through Thursday from 6:30am to 4:00pm . The examiner can also be reached on alternate Fridays.

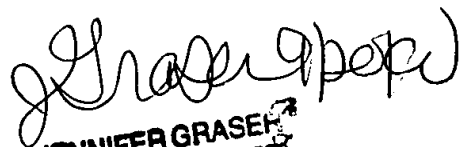
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If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette Smith, can be reached on (703) 308-3909. The fax phone number for the organization where this application or proceeding is assigned is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Ja-Na Hines 

September 14, 2000

  
JENNIFER GRASER  
PATENT EXAMINER